Review Article

Immunocontraceptive Vaccine- An Ore to Be Mined

K. Rajamanickam*, S. Gowrishankar[1] and V. Leela

Department of Veterinary Physiology, Madras Veterinary College, Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu, INDIA

[1]Department of Veterinary Parasitology

***Corresponding author:** rajapk92@gmail.com

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Abstract

Immunocontraception is the novel contraceptive approach, which uses body immune system to elicit an immune response to wedge the important steps in reproduction and reduce the fertility rate in vaccinated animals. Immunocontraceptives are developed mainly to target the three main areas of reproductive process namely gamete production, gamete function and gamete outcome. Contraceptive vaccines, which antagonize the effect of gonadotropin-releasing hormone (GnRH), follicular stimulating hormone (FSH) and luteinizing hormone (LH) have been tested in various species including dogs and cats. GnRH based vaccines are used for immune-castration of pigs to reduce the boar taint, which devalues the pork. Vaccines acting through the sperm-specific proteins and zona pellucida (ZP) glycoproteins have a greater advantage because of their high specificity to the germ cells. Immunization of dogs with native porcine ZP inhibit the fertility associated with ovarian dysfunction. Production of the monoclonal antibody against these proteins have added the advantage in immunocontraception. Recombinant ZP vaccines produced using Escherichia coli have reduced cross-reactivity with the somatic cells and impart long-term infertility. In spite of these advantages, immunocontraceptives may develop resistance in the immunized population in future, so more scientific inputs are required to increase the immunogenicity of immunocontraceptive vaccines and the novel vaccine delivery methods need to be developed which would impart long-term infertility with a single injection.

Key words: Immunocontraceptive Vaccine, Immune Response, Infertility, GnRh, ZP, Population Control

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Introduction

Traditionally, vaccines are used to impart immunity against various pathogens and protect animals from various diseases. Later, the approach was changed, scientists started to develop vaccines against diseases like cancer, autoimmune disorders, etc., as a therapeutic option and also aimed to neutralize negative

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factors against growth to promote growth in broilers by active immunizing against somatostatin (Guo *et al.*, 2013 and Anderson and Jabri, 2013). Recently, the trend was changed because the vaccines have been developed to impart infertility (contraception) in both animals and humans (Gupta *et al.*, 2014). Contraceptive vaccines are proposed to control population explosion, to prevent human-animal conflicts and to prevent zoonoses. In this kind of approach, preformed antibodies are produced to act on multiple targets and thus preventing fertilization. A contraceptive vaccine uses the host defence mechanism as a weapon to attack the normal reproductive functions as described Frayne and Hall (1999). When a contraceptive a vaccine is said to be successfully developed, it should meet the following criteria; it must be widely accepted, safe, easy to administer, affordable, reliable and should impart homogenous immune response in the subjects. Basically, contraceptive vaccines are of three types, I) acting on gamete production, II) acting on gamete function and III) acting on gamete outcome (Naz *et al.*, 2005).

Immunocontraception – A Concept of Magic Bullet

A novel approach developed in population control methods is "immunocontraception". Immunocontraceptives are vaccines that produce an adaptive immune response which makes the animal infertile. In various developing countries, the spread of zoonotic diseases is of increasing concern now and stray dogs are the important niche for the diseases like rabies. To control the population of stray dogs, castration and spaying are employed now but they are time-consuming and laborious in nature. In this regard herd immunization with the immunocontraceptive vaccines provide a better alternative approach. Comparing with other methods of population control, immunocontraceptives have ample advantages like long-term action, reduced endocrine disturbances have limited the need for implants and surgeries, etc., (Naz, 2011). Now researchers are focused on developing an immunocontraceptive vaccine which produces long-term infertility with single dose itself.

Immunocontraceptives Affecting Gamete Production

In reproductive physiology, gonadotropin-releasing hormone (GnRH) plays an important role. GnRH is produced from median eminence of hypothalamus and regulates the release of the follicular stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. They act on the gonads and regulates the production of gametes in both male and female animals. Immunoneutralization of these hormones will culminate the production of gametes by acting through ligand-receptor interactions. Immunocontraceptive vaccines which act on the gamete production are mainly of three types namely, GnRH based, FSH based and LH based immunocontraceptive vaccines Satish and Vidisha (2017).

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GnRH Based Immunocontraceptive Vaccines

Gonadotropin-releasing hormone is a decapeptide, that causes the release of gonadotropins in both the sexes. Hence a vaccine against GnRH can prevent fertilization in both male and female animals. GnRH has a main role in the hypothalamic-pituitary-gonadal axis besides its many extrapituitarial functions in testis, prostate and placenta (Naz, 2006). GnRH vaccines are validated on human subjects by the National Institute of Immunology, India, but the demerits have casted doubts for being used as a vaccine candidate (Schrater, 1995). Carrier proteins are antigenic molecules which are covalently attached to a poor antigen elicit a stronger immune response. Carrier proteins employed in the vaccine production play a major role in imparting antigenicity of the vaccine (Rino and Fabio, 2011). This is yet another area of focus to improve the efficacy of the vaccine. Initially various carrier proteins like diphtheria toxoid (DT) (Gupta *et al.,* 2014), Tetanus Toxoid (TT) (Hodges and Hearn, 1977), mycobacterium tuberculosis hsp 70 (Hannesdottir *et al.,* 2004), keyhole limpet hemocyanin (Miller *et al.,* 2000), thioredoxin (Stevens *et* al., 2005) and ovalbumin (Gupta *et al.,* 2014), were used in the production of vaccine but they imparted low antibody titre even after repeated injections. Diwan *et al.* (1998) and Ferro *et al.* (2004), tried an alternative approach with many adjuvant proteins/ peptides like Quil A, Aluminium hydroxide, polylactide co glycolide acid (PLGA), etc., among them GnRH-TT in polylactide co glycolide acid (PLGA) microspheres produced an effective immune response within 15 days of immunization, thus it nullifies the need of repeated injections. Vaxstrate, Improvac, Bopriva, Gonacon-Blue, Repro-BLOC, etc., are the few GnRH based contraceptives vaccines available in the market, but research is still on pipeline to evolve potential vaccines Kaur and Prabha (2014). Miller *et al.* (2013) described the GonaCon™ a commercial GnRH based contraceptive vaccine, consists of synthetic GnRH conjugated to KLH(blue protein from mollusc) developed by National Wildlife Research Center, USA, which was approved by Environment Protection Agency (EPA), USA for its use in white-tailed deer, burros and wild horse, which imparts two to five years of infertility in white-tailed deer by single injection itself, (Miller *et al.,* 2008). Benka and Levy (2015) validated the contraceptive efficacy of this vaccine was in cats also, where it produced infertility for about five months to five years depending upon the immune response developed in the respective queen or tom cats upon single injection. Massei *et al.* (2015) conducted a study using GnRH vaccine (Gonacon) to control the ferrel cattle population in Hong Kong to reduce the human-animal conflicts. The efficacy of the vaccine was assessed by measuring the anti-GnRH antibodies produced in the vaccinated herd. The results were on the positive side to make this vaccine as a commercial product. Improvac® is a GnRH based contraceptive vaccine, immunization of the Iberian female pigs reduced the incidence of standing oestrus, physiological competence of uterus and ovaries and serum progesterone level. After the third injection with Improvac®, 20 months of long-lasting immunity was observed in these pigs Dalmau *et al.* (2015). After injection of Improvac® in male pigs

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significant reduction in their sexual and aggressive behaviour was observed (Karaconji *et al.,* 2015). Active immunization of pubertal bulls with Bopriva® a GnRH based contraceptive vaccine, reduced the blood testosterone level, aggression and testicular growth Janet *et al.* (2012). In female dairy cattle, Bopriva® produces a significant reduction in the blood progesterone level, suppression of oestrus and reduced folliculogenesis (Balet *et al.,* 2014). Improvest®, an another commercial vaccine based on GnRH vaccine, which was used for imuno-castration in male pigs and to improve the meat quality by reducing the boar taint Lugar *et al.* (2017). In gilts this vaccine improved the growth performance and reduced the oestrum Bohrer *et al.* (2014). In general, loss of hair, atrophy of prostate, impotency after chronic exposure, inability to induce spermiation and abortion in pregnant animals in vaccinated subjects were considered to be a negative aspect of GnRH based immunocontraceptives.

FSH Based Immunocontraceptive Vaccines

Follicle stimulating hormone has two subunits alpha (α) and beta (β). It plays an important role in maintenance of spermatogenesis. Binding of FSH to the receptor is mediated by beta subunits. Researchers had exploited this function as a contraceptive in males. Mainly, antibodies developed against the ovine FSH was used as contraceptives in other species (Moudgal *et al.,* 1992), because the ovine FSH has the property of cross-reactivity with the FSH of other species including humans (Moudgal *et al.,* 1997). An added advantage in using the FSH based vaccine is, they will not react with LH and Thyroid Stimulating Hormone because of structural similarity with alpha subunit Moudgal *et al.* (1992). Moudgal *et al.* (1997) immunized male bonnet monkeys with the ovine FSH, they had no significant effect on blood testosterone level and they were reported with normal libido. When these animals were used for mating, they failed to impregnate the counterparts because this vaccine affects the spermatogenesis and reduces the fertility rate. But the immunized animals regained the fertility, when there was a decline in the anti-ovine FSH antibody level. To overcome this, scientists used FSH coding peptides for both priming and boosting instead of using native protein form. In this peptide – prime-boost strategies, there was also a reduction in the pathology of seminiferous tubules and interstitial cells Yang *et al.* (2011).

LH Based Immunocontraceptive Vaccines

Luteinizing hormone is the heterodimeric glycoprotein produced by the anterior pituitary gland. Main functions include induction of ovulation, corpus luteum development in females and production of testosterone in males. It is also called as interstitial cell-stimulating hormone in males. LH has one α and one β subunits. In ovine model, use of LH based vaccine inhibited the pregnancy for two breeding seasons. This is because of absence of ovulatory surge to induce ovulation. LH based contraceptives affect the production of sex steroids and lead to impotence in many subjects, this is considered to be a

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vital demerit in its usage Roberts and Reeves (1989). In another study by Remy *et al.* (1993), prepubertal male mice was immunized with baculovirus-expressed recombinant porcine LH receptor proteins showed significant reduction in spermatogenesis and testosterone level. The immunized mice had reduced fertility levels up to 75 percentage.

Sperm and Egg Specific Protein-Based Immunocontraceptive Vaccines

Successful interaction of sperm and egg is important for the formation of zygote. This process of interaction/fertilization is mediated by the specific proteins located on the egg and sperm cells. Immunocontraceptive vaccines have been developed to target these specific proteins present in both sperm and zona antigens of egg. In case of egg-specific proteins, zona pellucida proteins are exploited more for this purpose. In males, various sperm-specific proteins are identified and they are utilized for the production of immunocontraceptive vaccines. Less cross-reactivity with the somatic cell proteins and being non hormonal are the important hallmark of this type of vaccines.

Zona Pellucida (ZP) Proteins as Contraceptives

Zona pellucida (ZP) protein is a thick, translucent, glycoprotein present in the extracellular matrix of the oocyte. ZP protein serves as a docking site for recognition and tissue specificitis. ZP protein serves as a potential candidate in mediating fertilization process and for the sperm to bind with the oocyte. Post-translational modification of ZP leads to the formation of different families of Zona pellucida protein namely, ZP1, ZP2, ZP3 and ZP4 (Gupta *et al.*, 2003). ZP vaccines elicit humoral and/or cell-mediated immune response to inhibit the attachment of sperm to ovum because the binding sites are already occupied by the antibodies produced against the ZP protein in the immunized individuals. Inhibition of folliculogenesis in immunized individuals was due to immune response mediated by oophoritogenic T – cell epitopes (Satish *et al.*, 2011). ZP proteins also show cross-species reactivity (Kaur and Prabha, 2014). In rabbit model, infertility induced by the ZP vaccine is irreversible due to destruction of oocytes in all growing follicles Skinner *et al.* (1984). This shows another mechanism by which ZP vaccines induce the infertility apart from affecting sperm-egg interaction. Immunization of mare with native porcine ZP vaccine inhibited the anti-Mullerian hormone production and caused the suppression of ovarian follicular development and follicular function (Joone *et al.*, 2018). Initially, active immunization with native porcine ZP glycoproteins in both total solubilized and purified forms were employed to study the contraceptive potential of ZP proteins (Wood *et al.*, 1981). Mahi-Browm *et al.* (1982) demonstrated the use of total solubilized ZP proteins produced infertility but there was a significant side effect like abnormal cycles and ovarian pathology. These side effects were due to the contamination with other ovary associated proteins, also mediated by cytotoxic T lymphocytes and the use of Freund's adjuvants

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(Joone *et al.,* 2017). To reduce the side effects, the purified ZP glycoproteins including individual porcine ZP glycoproteins were developed without having any contamination with ovary associated proteins (Yurewicz *et al.,* 1987). *Escherichia coli* expressed recombinant dog ZP3 vaccine produced infertility in three out of four immunized dogs which was due to follicular atresia and atretic changes in ZP protein without any side effects (Santhanam *et al.,* 1998 and Srivastava *et al.,* 2002). To enhance the efficacy of ZP vaccine various strategies have been implemented they were-

1) Designing the immunogen by using multiple B epitope of single ZP or single epitope of multiple ZP proteins, this strategy inhibited the estrus in female dogs for longer time than usual (Cui *et al.,* 2010).
2) Altering the preparation methods of ZP vaccine like making microspheres using PLGA (poly D, L-Lactide-co-glycolide) (Kanchan and Panda, 2007), using the virus-like peptides (Grgacic and Anderson, 2006) and bacterial ghost (Walcher *et al.,* 2008) and using live vectors like attenuated *Salmonella typhimurium* (Zhang *et al.,* 1997).
3) DNA vaccine encoded with ZP protein sequence, these DNA based vaccines produced the bioactive antibodies (Leitner *et al.,* 1999). ZP based vaccines have non-hormonal actions, so they find greater utility and lesser side effects in contraceptive development. But ZP vaccines also have drawbacks like they can have contamination with ovarian associated proteins, batch to batch variation and limited ZP glycoprotein from native source.

Sperm Antigens as Contraceptive Vaccines

A contraceptive vaccine based on the sperm proteins is a promising candidate in developing an effective immunocontraception. Sperm has both iso and autoantigens in it, so cross immunization will produce anti-sperm antibodies (ASA) which reduces fertility. Successful fertilization of the oocyte by sperm depends on various factors like motility, viability, defects, capacitation and acrosomal reactions, penetration of ZP proteins and fusion with ovum. When any one of the above said phenomenon is targetted using specific antibodies, infertility is achieved. Sperm contains different types of proteins like sperm adhesion molecule (SPAM-1) (Cherr *et al.,* 2001), metalloprotease disintegrin cysteine (MDC) (Nishimura *et al.,* 2004), sperm protein (SP-10) (Herr *et al.,* 1990), fertilization antigen (FA-1) (Naz *et al.,*1984), Sperm protein – 17 (O'Rand and Porter, 1982), sperm agglutination antigen (SGA-1) (Diekman *et al.,*1997), sperm acrosomal membrane associated protein (SAMP-32) (Rao *et al.,* 2003) , lactate dehydrogenase (LDH-C_4) (O'Hern *et al.,* 1997), which are coded for specific function. Various technologies were implemented to use these proteins as antigens to elicit an immune response which includes genomics, proteomics, vaccinology, hybridization, hybridoma technology, gene knockout technology, etc. (Kaur and Prabha, 2014). Recombinant gene technology was also implemented using *E. coli* to produce sperm antigen-based immunocontraceptives. Passive immunization with either polyclonal

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or monoclonal antibodies developed against the sperm proteins (antigens) provided significant contraceptive response and reduced side effects (Reilly, 1999). Monoclonal antibodies (mAbs) produced against the rabbit sperm namely, mouse anti-rabbit sperm (MARS) showed greater contraceptive efficacy upon inseminating the female rabbits with sperm incubated with this mAbs (Castle *et al.*, 1997).

Immunocontraceptives Affecting Gamete Outcome

Fertilisation of sperm and ovum leads to the formation of the gamete. During various steps of pregnancy different types of factors were involved to maintain the viability of the gamete. Among them, human chorionic gonadotrphin (hCG) and Leukemia inhibitory factor (LIF) were considered to have crucial role (Lemons and Naz, 2011). Generation of antibodies against these factors will lead to termination of pregnancy (Kayisli *et al.*, 2003). hCG was produced from the tropoblast of pregnant women and they have two subunits namely, α and β subunits (Hearn *et al.*, 1988). Production of antibodies against the β -subunit of hCG produced the implantation failure in sub human primates (Naz, 2014). To increase the antigenicity of the hCG vaccine, recombinant approach was tried with tetanus toxin (Tandon *et al.*, 1981) and β -subunit of *Escherichia coli* heat-labile enterotoxin (Purswani and Talwar, 2011). LIF was a glycoprotein which belongs to the member of interleukin-6 cytokine family and it was considered to be an essential factor for implantation in different mammalian species (Robb *et al.*, 2002). Sengupta *et al.*, 2006 conducted a study in rhesus monkey by injecting the LIF antibody through intra-peritoneal route between days 3 and 4 after vaginal plug formation resulted in the blockade of embryo implantation. In another study by Lemons and Naz, 2012 there was an inhibition of fertility in the female mice immunized with LIF/LIF-R peptide vaccines and also there was a long-lasting circulating and local antibody response for the vaccine.

Advantages of Immunocontraceptives over Other Methods of Contraception

In previous days, contraception was done by using physical (surgery) and chemical methods (inclusive of endocrinal approach). In surgical approach, castration and spaying were implemented. In females, ovariohysterectomy can lead to complications like hemorrhage, stump pyometra, ovarian remnant syndrome, estrogen-responsive urinary incontinence, stump granuloma and fistula draining tracts. In case of castrated males, "irritable male syndrome" due to sudden withdrawal of testosterone and hernia are reported as complications (Lincoln, 2001 and Howe, 2006). In chemical method, intra-testicular injections of zinc gluconate and calcium chloride were used in males but the safety and efficacy need to be increased by conducting additional field trials (Levy *et al.*, 2008, Oliveira *et al.*, 2012, Fagundes *et al.*, 2014, Jana and Samanta, 2007). In the hormonal method, various hormonal agonists and antagonists are used, but they caused pathological lesions affecting the livability of the subjects Massei and Miller,

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(2013). As an alternative approach, immunocontraceptives have been developed in the recent years to reduce these disadvantages. They do not produce any reproductive tract pathology which is a life-threatening one, has a long-term immune response to reduce fertility and has little side effects. In some types of immunocontraceptive vaccines, a single administration is enough to elicit long-term infertility. This technique has been widely used to control the wildlife population explosion due to its easy administration; long-term effect with no surgical intervention is needed (Satish and Vidisha, 2017). Many commercial immunocontraceptive vaccines based on ZP and GnRH are evaluated in animals for its safety and efficacy. They are now proven to be a potential tool in imparting the contraception in animals (Naz and Saver, 2016). But despite of these ample advantages of immunocontraception for population control, this can evolve resistance among the population because the antibody response data from different studies indicated the low heritability for this trait suggesting that contraceptive resistant subjects will also have low heritability for their fertility levels. So we can anticipate the slow evolution of contraceptive resistant in the immunized population in future (Magiafoglou *et al.,* 2003).

Conclusion

In the new era of scientific development, the technology and science interplayed to produce many novel and innovative products. One such novel identification is the immunocontraceptives for controlling the population explosion. Immnuocontraceptives are now being widely employed in both animals and humans but more research activities are needed on this aspect to improve the efficacy and safety of the contraceptive vaccine usage. Exploitation of sperm antigens and zona pellucida proteins for the production of contraceptive vaccine should be done to improve the effectiveness in imparting contraception in animals. DNA vaccines based on ZP proteins show added advantage, also production of monoclonal antibodies against sperm antigen act as "cherry" on the top of the cake. So, immunocontraceptives vaccines provide an ample prospect to be used as tool in population control and unwanted pregnancies, an ore to be mined.

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